REMARKS

After entry of the above amendment, claims 1-54, 58-60, 63-76, 88-124, 127-143, and 145-147 will be pending in the present application. Applicants reserve the right to pursue subject matter no longer or not yet claimed in this or a related application.

Applicants respectfully request reconsideration in view of the amendment above and the following remarks.

Interview Summary

Applicants thank the Examiner for the telephonic interview on December 3, 2008, with Applicants' representative. The Examiner and Applicants' representative discussed possible amendments to overcome the art of record, as stated in the Interview Summary, mailed December 8, 2008.

Rejection under 35 USC Section 103

Claims 1-17, 19-27, 29-33, 35-37, 43-49, 51-52, 54, 64-70, 73-76, 124, 127, 146, and 147 were rejected under 35 USC 103(a) as unpatentable over Koster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980, 04/02/1996).

The Examiner stated that Koster teaches a method for sequencing a target nucleic acid, comprising the steps of fragmenting the target nucleic acid molecule to produce a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid, hybridizing the set to an array of nucleic acid probes to forma target array of nucleic acid molecules, wherein each probe comprises a single-stranded portion comprising a variable region, and the array comprises a collection of the probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination, determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the identified hybridized probes, determining the sequence of the target nucleic acid. The Examiner pointed out that Koster does not teach an array comprising a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination. (Final Office Action at page 8). The Examiner found that Cantor teaches an array and a probe with a single stranded variable region and the array comprises a collection of probes with sufficient sequence diversity

in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

The Examiner stated that "one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of probes with sequence diversity in the variable regions to hybridize all of the target sequence with nearly complete discrimination as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Koster in order to improve the analysis of the nucleic acid sequences." (Final Office Action at page 8).

The Examiner did not find Applicants' earlier argument to be persuasive. The Applicants pointed out that no prima facie case has been established. The Applicants argued that Koster teaches Sanger sequencing. Koster teaches determining the molecular weight of individual Sanger fragments and the comparison of the mass difference measured between the nested fragments with the known masses of each of the chain terminating nucleotides allows the sequence of each fragment to be determined. The instant methods do not rely on Sanger sequencing or production of a nested set of nucleic fragments, but rather the instant method relies on hybridization to an array of probes in which the molecular weight of the hybridized probes is measured to determine which probes have hybridized. The Examiner did not accept this argument, stating that this was "because "Applicants use the open language of comprising so it is permissible for Koster to teach an additional element in the method, specifically, Sanger sequencing." (Final Office Action at page 15).

In the interest of expediting prosecution, claims 1 and 124 have been amended without prejudice to their further prosecution. Claim 1 has been amended to include the language "consisting of" rather than "comprising." This language therefore excludes Sanger sequencing, as taught by Koster. Applicants also wish to point out existing language in claim 1, such as "based upon the identified hybridized probes, determining the sequence of the target nucleic acid," pointing to non-Sanger methods—identifying sequences by hybridization to known probes. Applicants therefore respectfully submit that claim 1, and claims rejected that are directly or indirectly dependent on claim 1, are allowable.

Claim 28 was rejected under 35 USC 103(a) as unpatentable over Koster, in view of Cantor, and in further view of Weiss. Applicants respectfully submit that Weiss does not provide the teaching missing in Koster and Cantor

Claim 34 was rejected under 35 USC 103(a) as unpatentable over Koster in view of Cantor. Applicants respectfully submit that in view of the present amendments, this rejection no longer applies.

Claims 71-72 were rejected under 35 USC 103(a) as unpatentable over Koster, in view of Cantor, and in further view of Sanghvi et al. (USPN 6,214,551 04/10/2001). Applicants respectfully submit that Weiss does not provide the teaching missing in Koster and Cantor.

Claims 38-39, 53, 58-60, 88, 89-124, 128-145 were rejected under 35 USC 103(a) over Koster in view of Cantor. Applicants respectfully submit that in view of the present amendments, this rejection no longer applies.

Applicants therefore respectfully request that claim 1, and claims directly or indirectly dependent thereto, claims 2-54, 58-60, 63-76, 88-123, 145-146, be allowed.

As to claim 124, and dependent claims 127, 129-143 and 147, Applicants respectfully submit that these claims should also be found allowable and that the rejection under 35 USC 103 be withdrawn.

Applicants have pointed out in previous arguments that the combination of the teachings of Koster with the teachings of Cantor does not result in the arrays and systems of these claims. The array of claim 124 requires that each probe include a single-stranded portion and a constant double-stranded portion and that the array includes a collection of probes with sufficient sequence diversity in the variable region to hybridize to all of the target nucleic acid molecule. The array also includes as an element that the array includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

As recognized by the Examiner, Koster does not teach or suggest an array of nucleic acid probes where each probe includes a single-stranded portion and a constant double-stranded portion, or an array of probes having sufficient sequence diversity in the variable regions to hybridize to all of the target nucleic acid molecule with complete or nearly complete discrimination, or probes that are about 10 to about 1000 nucleotides in length, or probes that include a variable region, or probes with a variable region of about 4-20 nucleotides in length. Applicants also respectfully submit that Koster does not teach or suggest an array of probes that includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

In the recent Final Office Action, the Examiner stated that mass modification "is used to discriminate between several samples of nucleic acids that are pooled together and analyzed at once. The discrimination of nucleic acids based on mass modification is using mass modification as a label. Labels are used to discriminate between for example nucleic acids and in this case mass modification is being used by Koster to discriminate between nucleic acids therefore the mass modification is serving as a means of labeling." (Final Office Action at page 15)

Applicants respectfully submit that even if Koster were to teach mass modification, the combination of Koster and Cantor do not render the present invention obvious. The instant methods do not rely on Sanger sequencing—instead, they rely on determining the sequence of hybridized nucleic acids by determining molecular weights of the nucleic acids that are hybridized to identified probes in a target array. Given that Koster teaches a method using Sanger sequencing, there is no motivation to combine Koster with Cantor, that teaches particular types of probes not needed for the Koster sequencing method.

Thus, Applicants respectfully submit that these claims are not prima facie obvious over the references cited by the Examiner, and respectfully request that this rejection be withdrawn.

Applicants respectfully submit that the claims are now in condition for allowance and request early notice thereof. Should the Examiner find that an interview would be of assistance, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

Dated: December 19, 2008 By: /Sheryl R. Silverstein/

Sheryl R. Silverstein
Registration No. 40,812

Grant Anderson, LLP
6640 Lusk Blvd., Suite C210
San Diego, California 92121

Direct: (760) 473-9472
Facsimile: (858) 623-3224